Chemoradiation can also be given to patients with locally unresectable disease or who are medically inoperable. In such cases, surgery with or without IORT can then be considered or additional lines of systemic therapy can be given.

If radiation therapy is to be used, conformal beam radiation should be the routine choice; intensity-modulated radiation therapy (IMRT), which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[335] should be reserved for unique clinical situations, such as unique anatomical situations or reirradiation of previously treated patients with recurrent disease.

Neoadjuvant Therapy for Resectable Colon Cancer

For the 2016 version of these guidelines, the panel added the option for neoadjuvant treatment with FOLFOX or CapeOx for patients with resectable, clinical T4b colon cancer. The randomized phase III FOxTROT trial is assessing whether this approach improves DFS (NCT00647530). Results from the feasibility phase of the trial were reported in 2012.[336] One hundred fifty patients with T3 (with ≥5 mm invasion beyond the muscularis propria) or T4 tumors were randomly assigned to 3 cycles of preoperative therapy (5-FU/LV/oxaliplatin), surgery, and 9 additional cycles of the same therapy or to surgery with 12 cycles of the same therapy given postoperatively. Preoperative therapy resulted in significant downstaging compared with postoperative therapy (P = .04), with acceptable toxicity.

Principles of the Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with colorectal cancer develop colorectal metastases,[337-339] and 80% to 90% of these patients have unresectable metastatic liver disease.[338,340-343] Metastatic disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver being the most common site of involvement.[344] However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.[343,345] Some evidence indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In a retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (P = .008) and more bilobar metastases (P = .016) than patients diagnosed with metachronous liver metastases.[346]

It has been estimated that more than half of patients who die of colorectal cancer have liver metastases at autopsy, with metastatic liver disease being the cause of death in most patients.[347] Reviews of autopsy reports of patients who died from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.[342] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[338,348] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of >3 tumors, and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with colorectal cancer.[345,349-353]

Other groups, including ESMO, have established guidelines for the treatment of metastatic colorectal cancer.[354] The NCCN recommendations are discussed below.

Surgical Management of Colorectal Metastases

Studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for a substantial number of these patients.[338,355]

Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,[350,353] and a recent meta-analysis reported a median 5-year survival of 38%.[356] In addition, retrospective analyses and meta-analyses have shown that patients with solitary liver metastases have a 5-year OS rate as high as 71% following resection.[357-359] Therefore, decisions relating to patient suitability, or potential suitability, and subsequent selection for metastatic colorectal surgery are critical junctures in the management of metastatic colorectal liver disease (discussed further in *Determining Resectability*).[360]

Colorectal metastatic disease sometimes occurs in the lung.[337] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.[201,361,362] Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases.[363-367]

Evidence supporting resection of extrahepatic metastases in patients with metastatic colorectal cancer is limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower than in patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.[368,369] However, a recent international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent resection of extrahepatic and hepatic disease remained disease-free at a median follow-up of 26 months, suggesting that concurrent resection may be of significant benefit in well-selected patients (ie, those with a smaller total number of metastases).[367] A recent systematic review concluded similarly that carefully selected patients might benefit from this approach.[370]

Data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.[371-375] However, in a retrospective analysis, 5-year survival was shown to decrease with each subsequent curative-intent surgery, and the presence of extrahepatic disease at the time of surgery was independently associated with a poor prognosis.[372] In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year OS and PFS rates were reported to be 73% and 22%, respectively.[371] A recent meta-analysis of 27 studies including >7200 patients found that those with longer disease-free intervals; those whose recurrences were solitary, smaller, or unilobular; and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.[376] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[362,375,377]

Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Resectable Synchronous Liver or Lung Metastases*. For patients presenting with unresectable metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver (discussed further in *Unresectable Synchronous Liver or Lung Metastases*).[378]

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. If resection is not feasible, image-guided ablation[379-381] or stereotactic body radiation therapy (SBRT; also called stereotactic

ablative radiotherapy [SABR])[341,382,383] are reasonable options, as discussed in subsequent paragraphs. Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins[381] or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that cannot be resected or ablated arterially, other locally directed treatment options may be offered.[384-386]

A meta-analysis of 90 studies concluded that hepatic arterial infusion (HAI), radioembolization, and transcatheter arterial chemoembolization (TACE) have similar efficacy in patients with unresectable colorectal metastases in the liver.[387] Local therapies are described in more detail below. The role of non-extirpative local therapies in the treatment of colorectal metastases remains controversial.

Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, HAI) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAI and intravenous 5-FU with or without LV was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.[342,388] The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcome in the group receiving HAI at later follow-up periods.[342,389] Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy was compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy.[342] Results of some studies also suggest that HAI may be useful in the conversion of patients from an unresectable to a resectable status.[390,391]

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[355] Limitations on the use of HAI therapy include the potential for biliary toxicity[342] and the requirement of specific technical expertise. Panel consensus is that HAI therapy should be considered selectively, and only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Arterially Directed Embolic Therapy

TACE involves hepatic artery catheterization to cause vessel occlusion with locally delivered chemotherapy.[385] A randomized trial using HAI to deliver drug-eluting beads loaded with irinotecan (DEBIRI) reported an OS benefit (22 months vs. 15 months; $P = .031$).[392] A 2013 meta-analysis identified 5 observational studies and 1 randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.[393] A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.[394] DEBIRI resulted in an improvement in the primary outcome measure of response rate (78% vs. 54% at 2 months; $P = .02$).

Doxorubicin-eluting beads have also been studied; the strongest data supporting their effectiveness come from several phase II trials in hepatocellular carcinoma.[395-400] A recent systematic review concluded that data are not strong enough to recommend TACE for the treatment of colorectal liver metastases except as part of a clinical trial.[401]

The panel believes that arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation (see *Radioembolization*, below) is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

Liver- or Lung-Directed Radiation

Local radiation therapies include arterial radioembolization with microspheres[402-412] and conformal (stereotactic) EBRT.[413]

EBRT to the metastatic site can be considered in highly selected cases in which the patient has a limited number of liver or lung metastases or the patient is symptomatic or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include three-dimensional conformal radiation therapy (CRT), SBRT,[341,382,383,414] and IMRT, which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.[335,415-418]

Radioembolization

A prospective, randomized, phase III trial of 44 patients showed that radioembolization combined with chemotherapy can lengthen time to progression in patients with liver-limited metastatic colorectal cancer following progression on initial therapy (2.1 vs. 4.5 months; $P = .03$).[419] The effect on the primary endpoint of time to liver progression was more pronounced (2.1 vs. 5.5 months; $P = .003$). Treatment of liver metastases with yttrium-90 glass radioembolization in a prospective, multicenter, phase II study resulted in a median PFS of 2.9 months for patients with colorectal primaries who were refractory to standard treatment.[420] In the refractory setting, a CEA level ≥90 and lymphovascular invasion at the time of primary resection were negative prognostic factors for OS.[411] Several large case series have been reported for yttrium-90 radioembolization in patients with refractory unresectable colorectal liver metastases, and the technique appears to be safe with some clinical benefit.[404,421,422]

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX+/- bevacizumab vs. FOLFOX+/- bevacizumab).[423] The trial assessed the safety and efficacy of yttrium-90 radioembolization as first-line therapy in 530 patients with colorectal liver metastases. Although the primary endpoint was not met, with PFS in the FOLFOX +/- bevacizumab arm at 10.2 months versus 10.7 months in the FOLFOX/Y-90 arm (HR, 0.93; 95% CI, 0.77–1.12; $P = .43$), a prolonged liver PFS was demonstrated for the study arm (20.5 months for the FOLFOX/Y90 arm vs. 12.6 months for the chemotherapy only arm; HR, 0.69; 95% CI, 0.55–0.90; $P = .002$).

Whereas very little data show any impact on patient survival and the data supporting its efficacy are limited, toxicity with radioembolization is relatively low.[423-426] Consensus amongst panel members is that arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

Tumor Ablation

Although resection is the standard approach for the local treatment of resectable metastatic disease, patients with liver or lung oligometastases can be considered for tumor ablation therapy.[427] Ablative techniques include radiofrequency ablation (RFA),[381,428] microwave ablation, cryoablation, percutaneous ethanol injection, and electro-coagulation. Evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and those with recurrent disease after hepatectomy with small liver metastases that can be

treated with clear margins is growing.[381,428-431] Data on ablative techniques other than RFA are extremely limited.[432-438]

A small number of retrospective studies have compared RFA with resection in the treatment of liver or lung metastases.[358,439-442] Most of these studies have shown RFA to be inferior to resection in terms of rates of local recurrence and 5-year OS.[439,443] Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, technologic limitations of RFA, or a combination of these factors is currently unclear.[441] A 2010 ASCO clinical evidence review determined that RFA has not been well-studied in the setting of colorectal cancer liver metastases, with no randomized controlled trials having been reported at that time.[438] The ASCO panel concluded that a compelling need exists for more research in this area. A 2012 Cochrane Database systematic review came to similar conclusions, as have separate meta-analyses.[436,437,444] Recently, a trial was reported in which 119 patients were randomized to systemic treatment or systemic treatment plus RFA with or without resection.[445] No difference in OS was seen, but PFS was improved at 3 years in the RFA group (27.6% vs. 10.6%; HR, 0.63; 95% CI, 0.42–0.95; P = .025). Similarly, 2 recent studies and a position paper by a panel of experts on ablation indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins.[379-381]

Resection or ablation (either alone or in combination with resection) should be reserved for patients with metastatic disease that is completely amenable to local therapy with adequate margins. Use of surgery, ablation, or the combination, with the goal of less-than-complete resection/ablation of all known sites of disease, is not recommended.

Peritoneal Carcinomatosis

Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis. Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.[95] The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and primarily consists of systemic therapy (see *Systemic Therapy for Advanced or Metastatic Disease*) with palliative surgery or stenting if needed for obstruction or impending obstruction.[446-448] If an R0 resection can be achieved, however, surgical resection of isolated peritoneal disease may be considered at experienced centers. The panel cautions that the use of bevacizumab in patients with colon or rectal stents is associated with a possible increased risk of bowel perforation.[449,450]

Cytoreductive Debulking with Hyperthermic Intraperitoneal Chemotherapy

Several surgical series and retrospective analyses have addressed the role of cytoreductive surgery (ie, peritoneal stripping surgery) in combination with perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.[451-459] In the only randomized controlled trial of this approach, Verwaal et al[460] randomized 105 patients to either standard therapy (5-FU/LV with or without palliative surgery) or to aggressive cytoreductive surgery and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients. OS was 12.6 months in the standard arm and 22.3 months in the HIPEC arm (P = .032). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this treatment as seen by follow-up results.[461] Importantly, this trial was

